**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Erickson et al.

Application No. 09/720,276

Filed: March 7, 2001

Art Unit: 1648

Examiner: Emily Le

For: FITNESS ASSAY AND
ASSOCIATED METHODS

**DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. HIROAKI MITSUYA**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Hiroaki Mitsuya, hereby declare and state that:

1. I have considerable experience in the area of anti-HIV drug therapy and the problems associated with HIV drug resistance. I received an M.D. in 1975, and a Ph.D. in 1982, from Kumamoto University School of Medicine. I have been conducting medical research at the National Institutes of Health for over twenty years, and specialize in anti-HIV research. I have authored over 250 articles relating to anti-HIV research and have been listed among the top 10 most cited AIDS researchers internationally. I am also on the Editorial Board of several scientific journals, including *Antiviral Research*, *Journal of Enzyme Inhibition*, and *Antiviral Chemistry & Chemotherapy*. I am currently Principal Investigator & Chief at the Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, of the National Cancer Institute. I am also Vice-Director at the University Hospital, National Kumamoto University School of Medicine. A copy of my Curriculum Vitae is attached.

2. I am a named inventor in the above-captioned patent application ("present application").

3. I have studied the efficacy of compounds known as "TMC-114" and "TMC-126" against multi-drug resistant HIV *in vitro*. TMC-114 and TMC-126 are the first and second

compounds, respectively, identified in Table 4, p. 81, of the present application. The antiviral efficacies of TMC-114 and TMC-126 were evaluated against a panel of multiply mutated, multi-drug resistant HIV strains obtained from infected human patients who were not responsive to existing anti-HIV regimens. The results of my research have been published in Koh et al., *Antimicrob. Agents Chemother.*, *47*, 3123-3129 (2003); and Yoshimura et al., *J. Virol.*, *76*, 1349-1358 (2002), copies of which are attached.

4. TMC-114 and TMC-126 exhibited extremely high and unprecedented broad-spectrum potency against all of the human strains of multi-drug resistant HIV tested in my laboratory. None of the drugs approved in the U.S. for human anti-HIV therapy have exhibited the broad-spectrum potency against multi-drug resistant HIV exhibited by TMC-114 and TMC-126.

5. Structure-based studies, including X-ray crystallographic studies on the enzyme-inhibitor complex, suggest that TMC-114 and TMC-126 interact with HIV protease in regions of the active site that known protease inhibitors do not interact with. The broad-spectrum potency of TMC-114 and TMC-126 against diverse strains of multi-drug resistant HIV is believed to be at least partially attributable to the ability of these compounds to uniquely interact with specific regions in the active site of HIV protease.

6. The research in this field as a whole, including my own research, demonstrates that TMC-114 and TMC-126 should effectively inhibit new strains of multi-drug resistant HIV that emerge in humans undergoing anti-HIV therapy.

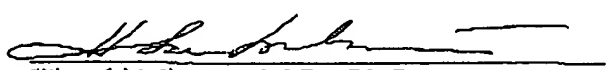
7. While it is believed that HIV ultimately can produce strains that are resistant to any existing anti-HIV agent (including TMC-114 and TMC-126), the research in this field as a whole, including my own research, demonstrates that TMC-114 and TMC-126 should significantly delay the emergence of HIV resistance *in vivo*. In this regard, TMC-114 and TMC-126 should significantly prolong the lives of HIV-infected humans who are at risk of dying as a result of multi-drug resistant HIV infection.

8. The research in this field as a whole, including my own research, demonstrates that TMC-114 and TMC-126 should be therapeutically effective for treating existing infections with multi-drug resistant HIV *in vivo*.

9. The present application provides biological data, e.g., multi-drug resistant HIV antiviral data, including the results of my own research, human protein binding studies, and *in vivo* data. The biological data provided by the present application, in view of the HIV protease inhibitor technology generally known in the art at the time that the present application was filed, demonstrate that the exemplified compounds should be therapeutically effective *in vivo*.

10. Clinical studies have confirmed that TMC-114 is in fact orally efficacious in humans for treating multi-drug -resistant HIV infection. The results of these clinical studies have been disclosed by Arasteh et al., 10th CROI, Feb 10-14, 2003, Session 4/Abst# 8, a copy of which is attached.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under/ 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

April 26, 2004 

Date Hiroaki Mitsuya, M.D., Ph.D.

# CURRICULUM VITAE
# Hiroaki Mitsuya, M.D., Ph.D.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|---|---|
| Present Address | 4601 North Park Avenue, #1010, Chevy Chase, MD 20815 |
| Phone | 301-657-1189 |
| Birth Date | August 9, 1950 |
| Birth Place | Sasebo, Nagasaki, Japan |
| Citizenship | Japan (US green card holder) |


Education

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| September 1982 | Received a Ph.D. degree (Doctor of Medical Science) from Kumamoto University School of Medicine, Honjo 1-1-1, Kumamoto 860, Japan |
| March 1975 | Received an M.D. degree from Kumamoto University School of Medicine |
| March 1969 | Graduated Sasebo North High School, Hachiman-Cho 6-31, Sasebo 857, Japan |

Work Experience

| | |
|---|---|
| July 2001 - Present | Principal Investigator & Chief, Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892 |
| April 2000 - Present | Vice-Director, University Hospital, National Kumamoto University School of Medicine, Kumamoto 860, Japan |
| April 2000-Present | Director, Department of Infectious Diseases, University Hospital, National Kumamoto University School of Medicine, Kumamoto 860, Japan |
| April 1998 - Present | Director, Center for Clinical Trials, University Hospital, National Kumamoto University School of Medicine, Kumamoto 860, Japan |
| April 1997 - Present | Professor of Medicine and Chairman, Department of Internal Medicine II, Kumamoto University School of Medicine, Kumamoto 860, Japan |

April 1997 - July 2001
Principal Investigator & Chief, Experimental Retrovirology Section, Medicine Branch, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892

July 1991 - March 1997
Chief, Experimental Retrovirology Section, Medicine Branch, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892

February 1989 - July 1991
Senior Investigator, Clinical Oncology Program, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892.

December 1988 - February 1989
Visiting Scientist, Clinical Oncology Program, National Cancer Institute

February 1984 - December 1988
Cancer Expert, Clinical Oncology Program, National Cancer Institute

October 1983 - February 1984
Visiting Fellow, Clinical Oncology Program, National Cancer Institute

October 1982 - September 1983
Visiting Fellow, Metabolism Branch, National Cancer Institute

February 1980 - September 1982
Instructor, Department of Internal Medicine II, Kumamoto University School of Medicine

April 1977 - January 1980
Research/Clinical Fellow, Department of Internal Medicine II, Kumamoto University School of Medicine

June 1975 - March 1977
Resident, Dept of Internal Medicine II, Kumamoto University School of Medicine

Editorial Boards

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|---|---|
| Editorial Board | *Antiviral Research*, April 1992 - present |
| Editorial Board | *Journal of Enzyme Inhibition*, April 1992 - present |
| Editor | Special Issue on "Inhibitors of HIV-1 Reverse Transcriptase and Protease as Therapeutics of AIDS", *Journal of Enzyme Inhibition*, April issue, 1992 |
| Editorial Board | *Antiviral Chemistry & Chemotherapy*, March 1993 - present |
| Editor | "Anti-HIV nucleosides: Past, Present, and Future", *Molecular Biology Intelligence Unit, R.G. Landes Company, Austin*, 1997. |
| Editorial Board | Critical Reviews in Oncology/Hematology (1998 - Present) |

Honors and Awards

American Society for Clinical Investigation (Member)

American Association of Immunologists

Fogarty International Visiting Fellow Scholarship, 1982-1983

Invention Award, National Cancer Institute, 1989

Special Act/Service Award, National Cancer Institute, 1990

US Department of Commerce Inventor's Awards -1987, 1989, 1989, 1989, 1990, 1991, 1992, 1995, 1996, 1996, 1996, 1997

NIH Director's Award, National Institutes of Health, 1992

"For important discoveries relating to infection with the human immunodeficiency virus and its therapy"

Outstanding Paper Award, Controlled Release Society, 1993

Anderson, B.D., Baker, D.C., Galinsky, R.E., Hoesterey, B.H., Morgan, M., Murakami, K., and Mitsuya, H.: Approaches toward the optimization of CNS uptake of anti-AIDS agents. *J. Controlled Release*, 19:219-230, 1992.

Among top 10 most cited AIDS researchers internationally, 1988-1992. Appearing in *Science* 260:1262, 1992.

NIH Intramural AIDS Targeted Antiviral Program Fund Award, 1993, 1994

Agents for Change Clinician Scientists Award 2000 (May 2000 in Stockholm; Glaxo-Wellcome) to: Yoshimura, K., Kato, R., Yusa, K., Kavlick, M.F., Maroun, V., Nguyen, A., Mimoto, T., Ueno, T., Shintani, M., Falloon, J., Masur, H., Hayashi, H., Erickson, J., and Mitsuya, H. (1999) JE-2147: a novel dipeptide protease inhibitor (PI) that potently inhibits multi-PI resistant HIV-1. *Proc. Natl. Acad. Sci. USA, 96:* 8675-8680.

Professional Activities (Selected)

American Federation for Clinical Research
American Association for the Advancement of Science
International Society of Antiviral Research

Special Review Committee for National Institute of Allergy and Infectious Diseases (NIAID) for evaluation of the Multicenter AIDS Cohort Study and Its Data Center, and the San Francisco Men's Health Study, 1991.

Session Organizer for the Gordon Research Conference on Chemotherapy of AIDS, Oxnard, California, March 15-20, 1992

Discussion Leader for the Gordon Research Conference on Chemotherapy of AIDS, Oxnard, California, March 22-26, 1993

International Scientific Advisory Board for the VIth International Antiviral Symposium, Nice, France, June 7-10, 1994

International Program Committee for the Xth International Conference on AIDS, Yokohamam, Japan, August 7-12, 1994

International Scientific Committee for the Conference on Overview and Status of HIV: The Disease, Prevention, and/or Control, Pavia, Italy, October 1-4, 1995

Co-organizer for the Conference on HIV-1 Infection and Cellular Metabolism, S. Patrignano, Corione, Italy, October 5 and 6, 1995

Organizing Committee, Ninth International Conference on Human Retrovirology: HTLV and related viruses, Kagoshima, April 5-9, 1999

Co-Chair, Special Task Force for Guidelines of Antiviral Therapy of HIV-1 Infecion, Japan. 1998 - Present.

Governing Council, International AIDS Society. 1999 - present.

Scientific Committee, HIV DART 2002, Frontiers in Drug Development fro Antiretroviral Therapipes, Naples, Florida, December 15-19, 2002.

Scientific Programme Committee, The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, July 13-17, 2003

International Program Committee for the XVth International Conference on AIDS, Bangkok, Thailand, July 11-16, 2004.

Other Responsibilities

Chairman, The Board of Directors, Washington, D.C. Japanese Language School (Non-profit Organization). January 1993 to December 1993

Selected Major Invited Lectureships

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| Plenary Speaker (Invited) | UCLA Symposium on "Human Retroviruses, Cancer, and AIDS: Approaches to Prevention and Therapy", Keystone, Colorado, April 1-6, 1987 |
| Plenary Speaker (Invited) | UCLA Symposium on "Mechanisms of Action and Therapeutic Applications of Biologicals in Cancer and Immune Deficiency Disorders", Keystone, Colorado, April 23-30, 1988 |
| Plenary Speaker (Invited) | FASEB Summer Conference on "Molecular Biology and Infectious Diseases", Copper Mountain, Colorado, July 17-22, 1988 |
| Plenary Speaker (Invited) | Symposium on Human Retroviruses and AIDS, Taipei, Republic of China, November 11-13, 1988 |
| Plenary Speaker (Invited) | UCLA Symposium on "Human Retroviruses", Tamarron, Colorado, February 4-11, 1989 |
| Speaker (Invited) | International Workshop on "Pathogenesis and Prevention of Hepatocellular Carcinoma", Oahu, Hawaii, February 13-15, 1989 |
| Speaker (Invited) | XIth International Symposium for Comparative Research on Leukemia and Related Diseases, Denver and Vail, Colorado, October 7-12, 1989 |
| Plenary Speaker (Invited) | Royal Society of Medicine Meeting on Applications of Biotechnology in Therapeutics and Preventive Medicine, Southampton, England, December 4-6, 1989 |
| Speaker (Invited) | First International Workshop on Viral Quantitation in HIV Infection, Paris, France, June 13-14, 1991 |
| Speaker and Session Organizer (Invited) | Gordon Research Conference on "Chemotherapy of AIDS", Oxnard, CA, March 15-20, 1992 |
| Plenary Speaker (Invited) | Vth World Conference on Clinical Pharmacology and Therapeutics, Yokohama, Japan, July 26-31, 1992 |
| Plenary Speaker (Invited) | First Asian Pacific Congress of Allergology and Immunology, Bangkok, Thailand, November 22-26, 1992 |

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| Speaker and Discussion Leader (Invited) | Gordon Research Conference on "Chemotherapy of |
| Plenary Speaker (Invited) | Keystone Symposium on "Frontiers in HIV Pathogenesis", Albuquerque, New Mexico, March 29-April 4, 1993 |
| Plenary Speaker (Invited) | 18th Int'l Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 1993 |
| Speaker (Invited) | Second International Workshop on Viral Quantitation in HIV Infection, Paris, France, June 3-4, 1993. |
| Speaker (Invited) | 1st International Meeting on Myotoxicity and Neurotoxicity of Antiretroviral Nucleotide Analogues, L'Aquila and Rome, Italy, March 19-25, 1994 |
| Speaker and Scientific Advisory Board | VIth International Antiviral (Invited) Symposium, Nice, France, June 7-10, 1994 |
| Round-Table Session Organizer and | Xth International Conference on International Program Committee (Invited) AIDS, Yokohama, Japan, August 7-12, 1994 |
| Speaker, Chairman, International Scientific Committee (Invited) | The Conference on Overview and Status of HIV: The Disease, Prevention, and Control, Pavia, Italy, October 1-4, 1995 |
| Co-organizer, Speaker, Chairman (Invited) | The First International Conference on HIV-1 Infection and Cellular Metabolism, S. Patrignano, Corione, Italy, October 5 and 6, 1995 |
| Speaker (Invited) | New Research Trends in Immunological Diseases, Second Green Cross International Symposium, Osaka, Japan, October 20-21, 1995. |
| Speaker (Invited) | Symposium on Molecular Insights into the Targets of HIV-1 Therapy. Stanford, California, May 10, 1996. |
| Speaker (Invited) | The Japanese Society for Investigative Dermatology 21st Annual Meeting, Tokyo, Japan, July 26-27, 1996. |

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| Speaker (Invited) | Course 6, "STD and AIDS" in the 19th World Congress of Dermatology, Sydney, Australia, June 15-20, 1997. |
| Speaker (Invited) | Japan-France AIDS Cooperative Study Conference, Tokyo, Japan, December 4-5, 1998 |
| Speaker (Invited) | International Symposium on HIV, Leukemia and Opportunistic Cancers, organized by Harvard AIDS Institute, May 23-28, 1999, Marrakech, Morocco |
| Speaker (Invited) | US-Japan AIDS Cooperative Study Conference, Toyama, Japan, March 17-19, 1999. |
| Speaker and Steering Committee | US-Japan AIDS Cooperative Study Conference, Santa Fe, March 17-19, 2000. |
| Speaker (Invited) and Advisory Board | 8th International Antiviral Symposium, Kagoshima, Japan, November 19-21, 2000. |
| Co-organizer | US-Japan AIDS Cooperative Study Conference, Kumamoto, March 21-24, 2001. |
| Speaker and Steering Committee | US-Japan AIDS Cooperative Study Conference, Seattle, WA, March 17-19, 2002. |
| Moderator | 26th International Congress of Internal Medicine, Kyoto, May 26-29, 2002 |
| Speaker (Invited) and Scientific Committee | HIV DART 2002: Frontiers in Drug Development of Antiretroviral Therapies, Naples, Florida, December 15-19, 2002 |
| Speaker and Steering Committee | US-Japan AIDS Cooperative Study Conference, Okinawa, Japan, March 5-7, 2003. |
| Speaker and Moderator | 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 11-15, 2003. |
| Moderator and Scientific Committee | The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, July 13-17, 2003 |
| Speaker and Steering Committee | US-Japan AIDS Cooperative Study Conference, Nashville, Tennessee, March 8-10, 2004. |

MAJOR REVIEWS:

1. MITSUYA, H. and Broder, S. Strategies for anti-retroviral therapy of patients with AIDS. *Nature*, 325:773-778, 1987.

2. MITSUYA, H., Yarchoan, R., and Broder, S.: Molecular targets for antiviral therapy against AIDS. *Science*, 249:1533-1544, 1990.

3. MITSUYA, H., Yarchoan, R., Kageyama, S., and Broder, S. Targeted therapy of human immunodeficiency virus-related disease. *FASEB J.* 5:2369-2381, 1991.

4. MITSUYA, H. Overview: Development of inhibitors of reverse transcriptase and protease as therapeutics against HIV infection. *J. Enzyme Inhibition*. 6:1-8, 1992.

5. MITSUYA, H. and Yarchoan, R. Development of antiretroviral therapy for AIDS and related disorders. In "*Textbook of AIDS Medicine*" (ed. Broder, S., Merigan, T., and Bolognesi, D.), Williams & Wilkins, Baltimore, pp. 721-742, 1994

6. Anderson, B.D. and MITSUYA, H, Reverse transcriptase as a target for AIDS therapy. In "*Design of Enzyme Inhibitors as Drugs, Volume 2*" (Ed. M. Sandler and H.J. Smith) Oxford University Press, Oxford, pp.290-332, 1994

7. MITSUYA, H. "*Anti-HIV nucleosides: Past, Present, and Futureç*, (Ed. H. Mitsuya), R.G. Landes Company, Austin, 1997.

8. MITSUYA, H. and Erickson, J. Discovery and development of antiretroviral therapeutics for HIV infection. *In*: Textbook of AIDS medicine, edited by Merigan, Bartlett, and Bolgnesi, Williams & Wilkins, Baltimore, *pp.* 751-780, 1999.

9. Kavlick, M.F. and MITSUYA, H. Emergence of drug resistant HIV-1 variants and their impact on antiretroviral therapy of HIV-1 infection. In "*The Art of Antiretroviral Therapy* " (Ed. Erik De Clercq) American Society for Microbiology, Washington, D.C. *pp.* 279-312, 2001

# Bibliography
# Hiroaki Mitsuya, M.D., Ph.D.


1. Kishimoto, S., Tomino, S., Inomata, K., Kotegawa, S., Saito, T., Kuroki, M., Mitsuya, H., and Hisamitsu, S.: Age-related changes in the subsets and functions of human T lymphocytes. *J. Immunol.* 121:1773-1770, 1978.

2. Mitsuya, H., Tomino, S., Hisamitsu, S., and Kishimoto, S.: Evidence for the failure of IgA specific T helper activity in a patient with immuno-deficiency with hyper-IgM. *J. Clin. Lab. Immunol.* 2:337-342, 1979.

3. Kishimoto, S., Tomino, S., Mitsuya, H., and Fujiwara, H.: Age-related changes in human suppressor T lymphocytes. *J. Immunol.* 123:1586-1593, 1979.

4. Kishimoto, S., Tomino, S., Mitsuya, H., Fujiwara, H., and Tsuda, H. Age-related decline in the *in-vitro* and *in-vivo* synthesis of antitetanus toxoid antibody in humans. *J. Immunol.* 125:2347-2353, 1980.

5. Kishimoto, S., and Mitsuya, H.: Immunosenescence and defense mechanisms. *Asian Medical J.* 23:558-563, 1980.

6. Mitsuya, H., Matsukura, M., Tomino, S., Fujiware, and Kishimoto, S.: T cell suppression of immunoglobulin synthesis in ataxia telangiectasia: Restruction of suppressor activity to B cells from unrelated donors. *Clin. Immunol. Immunopathol.* 19:383-393, 1981.

7. Mitsuya, H., Osaki, K., Tomino, S., Katsuki, T., and Kishimotor, S.: Patholophysiological analysis of peripheral blood lymphocytes from patients with primary immunodeficiency. I. Ig synthesis by peripheral blood lymphocytes stimulated with either pokeweek mitogen or Epstein-Barr virus *in-vitro*. *J. Immunol.* 127:311-315, 1981.

8. Kishimoto, S., Tomino, S., Mitsuya, H., and Nishimura, H.: Age-related decrease in frequencies of B-cell precursors and specific helper T cells involved in the IgG anti-tetanus toxoid antibody production in humans. *Clin. Immunol. Immunopathol.* 24:1-11, 1982.

9. Mitsuya, H.: Immunologic analysis of peripheral blood lymphocytes from patients with primary immunodeficiency. *J. Japanese Med.* (in English) 21:65-68, 1982.

10. Tomino, S., Fujiwara, H., Kagimoto, T., Mitsuya, H., Nishimura, H., and Kishimoto, S.: Decreased suppressor T cell activity in patients with hepatic cirrhosis (HC). *Clin. Exp. Immunol.* 48:625-632, 1982.

11. Mitsuya, H., Sato, M., Hirano, T., Fujimoto, K., Kawano, F., and Kishimoto, S.: Evidence for a malignant proliferation of IgE-class specific helper T cells in a patient

with Sezary syndrome exhibiting massive hyperimmunoglobulinema E. *Clin. Immunol. Immunopathol.* 26:171-183, 1983.

12. Matsuzaki, H., Yamaguchi, K., Hara, H., Mitsuya, H., Kawano, F., Araki, K., Tanaka, R., and Kishimotor, S.: Simultaneous occurrence of acute leukemia and multiple myeloma without previous chemotherapy. *Scand. J. Haematol.* 30:278-286, 1983.

13. Mitsuya, H., Matis, L., Megson, M., Bunn, P.A., Murray, C., Mann, D.L., Gallo, R.C., and Broder, S.: Generations of HLA-restricted cytotoxic T-cell line reactive against cultured tumor cells from a patient infected with human T-cell leukemia/lymphoma virus (HTLV). *J. Exp. Med.* 158:994-999, 1983.

14. Miyayama, H., Takemiya, M., Takahashi, K., Sasazaki, Y., Sato, M., and Mitsuya, H.: Massive IgE-hyperimmunoglobulinemia and storage histiocytosis in Sezary syndrome. *Cancer*, 53:1869-1877, 1984.

15. Mitsuya, H. and Broder, S.: Cytotoxic T cells specific for human T-cell leukemia/lymphoma virus (HTLV). In: *Human T cell Leukemia Virus*, (ed. Gallo RC, Essex M, Gross L) Cold Spring Harbor Laboratory, New York pp. 229-235, 1984.

16. Tsuchiya, H., Higuchi, S., Kuwahara, T., Matsuda, I., Mitsuya, H., and Yamaguchi, K.: Immunologic studies of peripheral blood in a child with hypogammaglobulinema. *Cancer*, 53:1492-1497, 1984.

17. Mitsuya, H., Matis, L.A., Megson, M., Cohen, O.J., Mann, D.L., Gallo, R.C., and Broder, S.: Immune T-cells reactive against human T-cell leukemia/lymphoma virus (HTLV). *Lancet*, i:649-652, 1984.

18. Mitsuya, H., Guo, H.G., Megson, M., Trainer, C., Reitz, M.S. Jr., and Broder, S.: Transformation and cytopathogenic effect in an immune human T-cell clone infected by HTLV-I. *Science*, 223:1293-1296, 1984.

19. Mitsuya, H., Guo, H.G., Cossman, J., Megson, M., Reitz, M.S. Jr., Broder, S.: Functional properties of antigen-specific T-cells infected by human T-cell leukemia-lymphoma virus (HTLV-I). *Science*, 225:1484-1486, 1984.

20. Mitsuya, H., Popovic, M., Yarchoan, R., Matsushita, S., Gallo, R.C., Broder, S.: Suramin protection of T cells *in vitro* against infectivity and cytopahic effect of HTLV-III. *Science*, 226:172-174, 1984.

21. Mitsuya, H., and Broder, S.: Clinical features of human T-cell leukemia/lymphoma virus (HTLV) associated T-cell neoplasma. In *Genetic and Phenotypic Markers of Tumors*. (Ed. P.K. Vogt) Plenum Press, New York, pp. 357-372, 1985.

22. Mitsuya, H. and Broder, S.: Human T-cell leukemia/lymphoma viruses (HTLV): A unique family of pathogenic retroviruses. *Curr. Top. Micobiol. Immunol.* 115:33-51, 1985.

23. Mitsuya, H., Matsushita, S., Harper, M.E., and Broder, S.: Pharmacologic inhibition of infectivity of HTLV-III *in vitro*. *Cancer Research*, 45:4583s-4587s, 1985.

24. Yarchoan, R., Mitsuya, H., Matsushita, S., and Broder, S.: Implication of the discovery of HTLV-III for the treatment of AIDS. *Cancer Research,* 45:4685s-4688s, 1985.

25. Tomita, S., Ambrus, J.L., Volkman, D.J., Longo, D.L., Mitsuya, H., Reitz, M.S. Jr., and Fauci, A.S.: Human T-cell leukemia/lymphoma virus (HTLV)-I transformation and subsequent cloning of normal human B cells: Direct responsiveness of cloned cells to recombinant interleukin 2 by differentiation in the absence of enhanced proliferation. *J. Exp. Med.* 162:393-398, 1985.

26. Broder, S., Yarchoan, R., Collins, J.M., Lane, H.C., Marcham, P.D., Klecker, R.W., Redfield, R.R., Mitsuya, H., Hotch, D.F., Gelmann, E., Groopman, J.E., Resnick, L., Gallo, R., Myers, C.E., and Fauci, C.E.: Effects of suramin on HTLV-III/LAV infection presenting as Kaposi's sarcoma or AIDS-related complex: Clinical pharmacology and suppression of virus replication *in vivo*. *Lancet*, ii, 627-630, 1985.

27. Mitsuya, H., Weinhold, K.J., Furman, P.A., St. Clair, M.H., Lehrman, S.N., Gallo, R.C., Bolognesi, D., Barry, D.W., and Broder, S.: 3'-azido-3'-deoxy-thymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*. *Proc. Natl. Acad. Sci. USA*. 82:7096-7100, 1985.

28. Mitsuya, H., Matsushita, S., Yarchoan, R., and Broder, S.: Protection of T-cells against infectivity and cytopathic effect of HTLV-III *in vitro*. In: *Retroviruses in Human Lymphoma/Leukemia*. ed. M. Miwa et al. Japan Sci. Soc. Press, Tokyo/VNU Science Press, Utrecht, pp. 277-288, 1985.

29. Jarrett, R.F., Mitsuya, H., Mann, D.L., Cossman, J., Broder, S., Gallo, R.C., and Reitz, M.S.: Configuration and expression of the gene encoding the b-chain of the T-cell receptor in HTLV-I infected cells. *J. Exp. Med.* 163:383-399, 1986.

30. Mitsuya, H., and Broder, S.: Inhibition of the *in vitro* infectivity and cytopathic effect of HTLV-III/LAV by 2', 3'-dideoxynucleosides. *Proc. Natl. Acad. Sci. USA.* 83:1911-1915, 1986.

31. Matsushita, S., Robert-Guroff, M., Trepel, J., Cossman, J., Mitsuya, H., and Broder, S.: Human monoclonal antibody against an envelope glycoprotein of human T-cell leukemai virus type-I. *Proc. Natl. Acad. Sci. USA.* 83:2672-2676, 1986.

32. Kotani, H., Mitsuya, H., Jarrett, R.F., James, S.P., and Strober, W.: An autoreactive T cell clone which can be activated to provide both helper and suppressor function. *J. Immunol.* 136:1951-1959,1986.

33. Yarchoan, R., Klecker, R.W., Weinhold, K.J., Durack, D.T., Gelmann, E.D., Lehrman, S.N., Blum, R.M., Barry, D.W., Shearer, G.M., Fischl, M.A., Mitsuya, H., Gallo, R.C., Collins, J.M., Bolognesi, D.P., Myers, C.E., and Broder, S.: Treatment of AIDS or AIDS-related complex with 3'-azido-3'-deoxythymidine, an inhibitor of HTLV-III/LAV replication. *Lancet,* i:575-580, 1986.

34. Balzarini, J., Mitsuya, H., Cleron, E.D., and Broder, S.: Comparative inhibitory effects of suramin and other selected compounds on the infectivity and replication of human T-cell lymphotropic virus (HTLV-III)/lymphadenopathy-associated virus (LAV). *Int. J. Cancer*, 37:451-457, 1986.

35. Balzarini, J., Mitsuya, H., Clercq, E.D., and Broder, S.: Aurintricarboxylic acid and evans blue represent two different classes of antionic compounds which selectively inhibit the cytopathic effect of human T-lymphotropic virus/lymphadenopathy-associated virus. *Biochem. Biophy. Res. Commun.* 136:64-71, 1986.

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# First Clinical Results on Antiretroviral Activity, Pharmacokinetics, and Safety of TMC114, an HIV-1 Protease Inhibitor, in Multiple PI-experienced Patients

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**Background:** TMC114 is a Protease Inhibitor (PI) with potent in vitro antiviral activity against wild-type and PI-resistant HIV-1. The study objective was to evaluate the activity, safety, and pharmacokinetics of TMC114 with low dose ritonavir (TMC114/r) in multiple PI-experienced patients (pts) currently failing a PI-containing regimen at study entry.

**Methods:** Open, randomized Phase IIa study in 50 multiple PI-experienced pts. TMC114/r was substituted for the failing PI(s); all other ARVs were not changed. Pts received TMC114/r at doses of 300/100 mg bid (A: n = 13), 600/100 mg bid (B: n = 12), 900/100 mg qd (C: n = 13) or continued the failing regimen (D: n = 12). Pts received TMC114/r for 14 days after which it was discontinued and changes in ART were permitted.

**Results:** Median baseline plasma HIV-1 RNA for the study group was 4.3 log10 and median baseline CD4 cell count was 297/μL. Median number of previously used PIs was: A:3, B:3, C:4, D:3. Median number of PIs within the range of drug susceptibility (Antivirogram) was A:1, B:1, C:0, and D:1. The median number of primary PI mutations was A:7, B:6, C:7, and D:8. In the ITT analysis, the median change in plasma HIV-1 RNA (log10) from baseline to day 14 in arms A, B, C and D was -1.24, -1.50, -1.13 and +0.02 ($p < 0.001$). The range of HIV-1 RNA reduction in the treatment arms was -0.47 to -2.5 log10 (median -1.35). In arms A, B, C, and D, 69%, 92%, 69%, and 17% had at least a 1.0 log10 reduction in HIV-1

RNA, respectively, and in the TMC114/r groups, 97% had at least a 0.50 log10 reduction from baseline.
Median TMC114 Cmin and AUC24h at day 14 in Arms A, B, and C were 1.2 μg/ml and 53.3 μg.h/ml, 1.4 μg/ml and 60.4 μg.h/ml, and 1.6 μg/ml and 67.9 μg.h/ml, respectively.
Treatment with TMC114/r was generally well tolerated. The most commonly reported AEs were GI events. One (1) pt in arm C discontinued treatment due to GI discomfort and 1 pt in arm B had an SAE (hepatitis). Overall, in the TMC114/r arms, 2, 2, and 1 pts had a grade 3/4 ALT, AST or GGT elevations, respectively. One (1) pt in the control group had a grade 3 AST.

**Conclusions:** TMC114/r exhibited potent antiretroviral activity and favorable pharmacokinetics when given for 14 days to multiple PI-experienced pts currently failing a PI-containing regimen. For the TMC114/r arms, maximum and median changes in HIV-1 RNA (log10) were -2.49 and -1.35 copies/ml, respectively. TMC114/r was generally well tolerated.